UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C.. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/897,441	07/21/1997	MATHIAS FIBI	5552.0953-04	4501

22852 7590 03/12/2002

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/897,441	Fibi et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7, 9-12, and 14-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9, 14-16, and 22* is/are allowed.

6)☒ Claim(s) *5-7, 10-12, 17-21, and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18)☐ Interview Summary (PTO-413) Paper No(s). _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

Response to Arguments

1. Claims 5-7, 9-12, 14-23 are pending and under consideration.

Claim Rejections Maintained

2. The rejection of claims 17-19 under 35 U.S.C. 102(b) as being anticipated by Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) is maintained for reasons of record. Applicant argues that Sytkowski et al teaches against the isolated proteins directly binding to the EPO receptor as it is concluded on page 1162, "Thus, it appears that none of these peptides react directly with the erythropoietin receptor". Firstly, claim 17 is drawn to an antibody which binds to an epitope which binds to the EPO receptor and as such does not specify that an isolated peptide used to simulate an epitope of the full length EPO protein must bind to the EPO receptor in vitro and elicit a biological effect. Further, the binding of other epitopes, not included in the isolated peptide used to raise the antibody may be necessary for increasing the binding affinity of the isolated peptide by altering the steric interaction of residues with the EPO receptor. Philo et al (Biochemistry, 1996, Vol. 35, pp. 1681-1691) teach that EPO has two independent binding sites for the EPO receptor, one governed by a high affinity interaction and the other governed by a lower-affinity interaction. Narhi et al (Journal of Protein Chemistry, 1997, Vol. 16, pp. 213-225) teach that occupation of the first binding site results in a conformational change of the EPO/EPO receptor complex.. Philo et al teach that the second binding interaction is quite weak and dissociated during chromatography. Philo et al concludes that binding studies with full length EPO and the EPO receptor cannot rule out sequential binding models. Thus given the teachings of Philo et al and Narhi et al on the complexity of the interaction between EPO and its receptor, and the weakness of the interaction of second binding site with the EPO receptor, it is reasonable to conclude that in vitro studies designed to measure activation or inhibition based on contacting isolated peptides consisting of amino acid residues of 99-118 and 111-129 with the EPO receptor do not rule out the possibility that these amino acid residues when within the full length EPO protein directly bind to the EPO receptor.

3. The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al (Journal of Biological Chemistry, 1987, Vol. 262, pp. 1161-1165) in view of Yanagawa et al (Blood, 1984, Vol. 64, pp. 357-364) is maintained for reasons of record.. Applicants argue that the rejection as it is based on Sytkowski et al is faulty. Applicants further argue that the teachings of Yanagawa et al have been misinterpreted as the work of Yanagawa et al was directed to monoclonal anybodies which bound to contaminants in the EPO preparation. This has been considered but not found persuasive. Yanagawa et al teach the production of three hybridomas secreting antibodies which bind to erythropoietin, one of which exhibited a high growth rate and production of antibody. Yanagawa et al further teach that this monoclonal antibody will be useful for the purification of erythropoietin.

4. The rejection of claims 5, 6, 11, 12, 17, 20 and 23 under 35 U.S.C. 102(b) as being anticipated by Lin (US 4,703,008) is maintained for reasons of record. Applicants argue that Lin does not disclose that the antibodies bound to epitopes which bound to the EPO receptor. Applicants argue that Lin teaches against this concept as Lin states "Preliminary in vivo activity studies on the three peptides revealed no significant activity either alone or in combination." Applicants argue that the addition of eight amino acids to the peptide used by Lin to generate polyclonal antibodies may affect the ability of the resulting peptides to elicit the antibodies of the invention. This has been considered but not found persuasive. The statement by Lin et al does not constitute evidence that the peptide 144-166 of EPO does not bind directly to the EPO receptor. Firstly, claims 5 and 6 are draw in part to methods of using an EPO peptide for the preparation of epitope-specific anti-EPO antibodies, wherein said EPO peptide consists essentially of amino acid residues 152-166 of EPO. Claim 6 further specifies that the antibodies neutralize the biological activity of EPO. Lin does not specifically disclose that the polyclonal antibodies obtained by immunization with the 144-166 peptide have EPO neutralizing activity. However, it is reasonable to conclude that some of the antibodies which constitute the polyclonal antibodies made by Lin would have the property of reacting with the epitope of EPO consisting of residues

152-166, as these amino acids are included in residues 144-166 and that these antibodies would inherently be neutralizing antibodies, as the specification teaches that the property of binding to residues 152-166 of EPO is commensurate with the property of a neutralizing antibody.

Claim 17 does not specify that the isolated peptide used to simulate an epitope of the full length EPO protein must bind to the EPO receptor in vivo and elicit a biological effect. There are many reasons why a peptide administered in vivo would not elicit the same biological effect of the parent protein. Firstly, the peptide, out of context of the EPO protein may be rapidly degraded in vivo before binding to the EPO receptor. Secondly, the binding of other epitopes, not included in the peptide used to raise an antibody, may be necessary for increasing the binding affinity of the isolated peptide by altering the steric interaction of residues 144-166 with the EPO receptor, for the reasons given in Philo et al and Narhi et al, supra. The specification teaches that the peptide 152-166 represents an amino acid sequence within EPO which directly binds to the EPO receptor. The peptide used by Lin, 144-166, is the same amino acid sequence with the addition of the eight amino acid sequences which are normally attached to the animo terminus of the 152-166 sequence in the full length EPO protein. As 152-166 directly binds the EPO receptor, it is reasonable to conclude that 144-166 also directly binds to the EPO receptor as it contains the 152-166 sequence in addition to adjacent amino acid sequences present in EPO. Additionally, it is reasonable to conclude that some of the antibodies which constitute the polyclonal antibodies made by Lin would have the property of reacting with the epitope of EPO consisting of residues 152-166, as these amino acids are included in residues 144-166. Further any antibodies which would bind to the residues of 152-166 of EPO would inherently be neutralizing antibodies, as the specification teaches that the property of binding to residues 152-166 of EPO is commensurate with the property of a neutralizing antibody.

5. The rejection of claims 6, 7, 11, 17-21 for obviousness-type double patenting over claims 1 and 2 of USP 5,712,370 is maintained for reasons of record.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
March 11, 2002